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AMENDMENTS

In the Claims:

Please cancel claims 1-10 without prejudice or disclaimer.

REMARKS

I. Status of the Claims

Claims 1-40 are pending in the application. Claims 1-4, 7-13 and 16-40 are rejected under 35 U.S.C. §103(a) as allegedly obvious over Murrer *et al.* ("Murrer '134") in view of Narasimhan *et al.* ("Narasimhan"). Claims 1-40 stand rejected under §103 as allegedly obvious over Narasimhan, Collery *et al.* ("Collery '598") and Bernstein '088. Claims 1-10 have been canceled; claims 11-40 are therefore presented for reconsideration. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Rejections Under §103

A. Murrer '134 in view of Narasimhan

Claims 1-4, 7-13 and 16-40 are rejected under 35 U.S.C. §103(a) as allegedly obvious over Murrer '134 in view of Narasimhan. Murrer '134 is cited as teaching the use of gallium complexes to treat HIV. Narasimhan is cited as teaching that gallium inhibits ribonucleotide reductase. The examiner also relies on the facts (a) T lymphocytes are lost when infected with HIV, and (b) ribonucleotide reductase inhibitors are currently used in combination therapies for HIV. While the examiner acknowledges that the prior art fails to disclose a method of treating HIV with gallium, it is argued that "the prior art amply suggests the same as it is know that

compositions containing gallium are effect against HIV and ... [that] gallium is a ribonucleotide reductase inhibitor and that ribonucleotide reductase inhibitors potentiate the effects of dideoxynucleotides." Applicants traverse.

As with every obviousness analysis, it is of critical importance that one not lose sight of the requirements for a valid *prima facie* case. Those requirements are aptly spelled out in *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed Cir. 1991). In that case, the Federal Circuit stated that in order to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. See also *Manual of Patent Examining Procedure* §2142.

It is not disputed that Narasimhan discloses that gallium inhibits ribonucleotide reductase. In addition, it is also worth noting that gallium nitrate was shown to inhibit reverse transcriptase as early as 1974. See Collery '598, col. 1, lines 28-32. However, one cannot overlook the fact that Narasimhan fails to mention anything regarding anti-viral applications, much less about HIV therapy. Thus, motivation to use gallium as an anti-HIV therapeutic must come from somewhere else.

On the other hand, Murrer '134 clearly adddresses HIV therapies:

> We have now discovered certain polyoxometallate compounds which exhibit not only activity against HIV in the screening tests used, but also relatively low toxicity against cells. Accordingly, the present invention provides as active compound for the various aspects of the invention, a compound selected from those containing ions of the Keggin structure, an defined by the general formula:
>
> $$A_x[MDLW_{11}]_{39}.yH_20 \qquad (I)$$

$$A_x[D'(MW_{11}O_{39})_2].yH_20 \qquad \text{(Ia)}$$

...

D is a metal and D' is a lanthanide in oxidation state 3 or 4,

....

Col. 2, lines 18-37. Moreover, the ***only explicit mention*** of gallium in the entire Murrer '134 patent is at col. 3, where gallium is listed as one of ***ten possible metal ions***, and in Table (columns ¾), where two gallium-containing compounds were tested (out of 15 other compounds "according to the invention"). Applicants respectfully submit that one of skill in the art, reading this document, would find ***nothing*** to suggest that ***gallium itself acts as an antiviral agent***. To the contrary, gallium appears to be nothing more than one of a variety of non-critical metal ions that are inconsequential to the activity of the overall compounds.

Now, returning to the *Vaeck* factors set out above, applicants submit that the examiner has not identified, ***in the prior art***, the appropriate motivation to select gallium as a primary therapeutic agent. *In re Soli*, 137 USPQ 797 (CCPA 1963). All the cited art teaches is (a) a biological activity of gallium with no mention of utility, and (b) anti-viral compositions which happen to optionally include gallium. The examiner has, in this situation, apparently used applicants' own disclosure to provide the motivation, which is improper. *In re Carroll*, 202 USPQ 571 (CCPA 1979) ("One of the more difficult aspects of resolving questions of non-obviousness is the necessity 'to guard against slipping into the use of hindsight"). Though some "hindsight" is required in order to properly search the invention, once the most relevant art has been identified, the examiner must establish that the requisite motivation exists ***in the cited art***. As above explained, the art fails in this regard.

It also is worth stating that the prior art says nothing about the ability of gallium, as a therapeutic agent, to inhibit HIV. While the compounds of Murrer '134 were shown to have *in*

vitro effects, these were not gallium *per se*, but compounds that contained gallium ***in the context of polyoxymetallates***. As such, this reference says little, if anything, regarding the efficacy of gallium to treat HIV. Narashimhan is notably silent on treatments, and cannot therefore provide any meaningful comment on the issue of likelihood of success.

In conclusion, applicants respectfully submit that the references, even when viewed in combination, fail to appropriately suggest that one could use gallium as an anti-HIV therapy, much less use it successfully. As such, applicants respectfully submit that the rejection is founded on an improper obviousness analysis, and thus a *prima facie* case has not been established. Reconsideration and withdrawal of the rejection is therefore requested.

B. Narashimhan, Collery '598 and Bernstein '088

Claims 1-40 stand rejected under §103 as allegedly obvious over Narashimhan, Collery '598 and Bernstein '088. Narashimhan is cited as above. Bernstein, as implicitly acknowledged, only deals with gallium formulations and says nothing about HIV. Thus, the critical reference here is Collery '598, which is cited by the examiner as teaching that "gallium complexes are effective at treating HIV and that gallium nitrate inhibits reverse transcriptase found in retroviruses, such as HIV." While the examiner acknowledges that the prior art fails to disclose a method of treating HIV with gallium, it is argued that "the prior art amply suggests the same as it is know that compositions containing gallium are effect against HIV and ... [that] gallium is a ribonucleotide reductase inhibitor and that ribonucleotide reductase inhibitors potentiate the effects of dideoxynucleotides." Applicants traverse.

This rejection is very similar to that advanced up with two exceptions: (a) Narashimhan is used as the primary reference and (b) Bernstein '088 is cited to support rejection of certain

dependent claims. Otherwise, the reasoning appears to be precisely the same. That said, applicants again point out that despite the teachings of Narashimhan, that reference fails to mention anything regarding anti-viral applications, much less about HIV therapy. Thus, motivation to use gallium as an anti-HIV therapeutic must come from somewhere else.

Collery '598, on the other hand, very clearly describes the possibility of HIV therapies: "It has now been found that certain gallium (III) complexes have antitumor and antiviral activities. The invention gallium (III) complexes comprise gallium (III) complexes of N-heterocycles." Col. 1, lines 39-43. Thus, far from focusing on gallium, Collery '598 discusses a complex heterocyclic compound that contains, as one aspect, gallium (III) ions. Moreover, there is only marginal information in Collery '598 on the activity of these compounds, and what information there is suggests that these compounds are far less effective at inhibiting HIV (low EC_{50}/IC_{50} ratio) that existing drugs such as AZT. Notably, the issued claims in Collery '598 ***are limited to use of these compounds to treating tumors***. Applicants respectfully submit that one of skill in the art, reading this document, would find very little to suggest that ***gallium itself acts as an antiviral agent*** without being part of a more complex compound, and in fact, one would doubt its efficacy even in that environment.

Now, returning to the *Vaeck* factors set out above, applicants submit that the examiner has not identified, ***in the prior art***, the appropriate motivation to select gallium as a primary therapeutic agent. *In re Soli*, *supra*. All the cited art teaches is (a) a biological activity of gallium with no mention of utility, and (b) compositions which include gallium in the context of a N-heterocycles which have dubious antiviral properties. The examiner has, again, apparently used applicants' own disclosure to provide the motivation, which is improper. *In re Carroll*, *supra*. Though some "hindsight" is required in order to properly search the invention, once the

most relevant art has been identified, the examiner must establish that the requisite motivation exists ***in the cited art***. As above explained, the art fails in this regard.

It also is worth stating that the prior art does not provide sufficient information regarding the ability of gallium to act as a therapeutic agent against HIV. While the compounds of Collery '598 were shown to have marginal *in vitro* effects, these were not gallium *per se*, but compounds that contained gallium ***in the context of N-heterocycles***. As such, this reference says little, if anything, regarding the efficacy of gallium (or even gallium-containing N-heterocycles) to treat HIV. Narasimhan is notably silent on treatments, and cannot therefore provide any meaningful comment on the issue of likelihood of success.

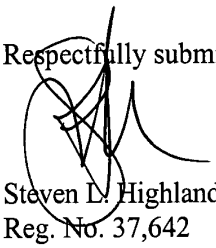
In conclusion, applicants respectfully submit that the references, even when viewed in combination, fail to appropriately suggest that one could use gallium as an anti-HIV therapy, much less use it successfully. As such, applicants respectfully submit that the rejection is founded on an improper obviousness analysis, and thus a *prima facie* case has not been established. Reconsideration and withdrawal of the rejection is therefore requested.

III. Conclusion

In light of the foregoing comments, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should the examiner have any questions regarding this response, a telephone call to the undersigned is invited.

Please date stamp and return the enclosed postcard as evidence of receipt.

Respectfully submitted,



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Date: February 4, 2003

APPENDIX A: MARKED UP COPY OF AMENDED CLAIMS

1. (Canceled) A method of inhibiting human immunodeficiency virus (HIV) ribonucleotide reductase (Rr) in a subject infected with HIV comprising administering to said subject an amount of a gallium composition effective to inhibit Rr.

2. (Canceled) The method of claim 1, wherein HIV is HIV-1.

3. (Canceled) The method of claim 1, wherein HIV is HIV-2.

4. (Canceled) The method of claim 1, wherein HIV has infected a T-cell.

5. (Canceled) The method of claim 1, wherein said gallium composition is gallium nitrate.

6. (Canceled) The method of claim 1, wherein said gallium composition is a gallium-hydroxypyrone complex.

7. (Canceled) A method of inhibiting human immunodeficiency virus (HIV) replication in a subject infected with HIV comprising administering to said subject an amount of a gallium composition effective to inhibit HIV replication.

8. (Canceled) The method of claim 7, wherein HIV is HIV-1.

9. (Canceled) The method of claim 7, wherein HIV is HIV-2.

10. (Canceled) The method of claim 1, wherein HIV has infected a T-cell.